PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Electronic Patient-Generated Health Data to Facilitate Prevention and Health Promotion: A Scoping Review Protocol
AUTHORS	Nittas, Vasileios; Mütsch, Margot; Ehrler, Frederic; Puhan, Milo

VERSION 1 – REVIEW

REVIEWER	Isomi Miake-Lye VA Greater Los Angeles Healthcare System, USA
REVIEW RETURNED	22-Jan-2018

GENERAL COMMENTS	The rapidly growing area of electronic patient-generated health data provides both opportunities and challenges for the authors of this protocol. There is great potential for scientific contribution from this scoping review. The most serious concern this raises is whether the large amount of published information I anticipate the team will find will be amenable to the protocol described. While such a large and detailed review would be valuable, is it feasible? Has the team run preliminary searches that might indicate the magnitude of evidence they are expecting to synthesize? Aside from this overarching concern, a few more specific suggestions are below: 1. In the title it would be more accurate to call this a scoping review protocol, rather than a systematic scoping review protocol. 2. There is some wording clarification that would be helpful for the language that repeats related to the study objectives: “generation, share, utilization, context and impact” appears a few times. I suggest each of these being its own question to help bring clarity to this phrase. I currently am not sure what each means, which may be influencing some of my later suggestions. In addition, the phrasing in the abstract is different than how it appears in the manuscript, so once a phrasing is chosen, it would be helpful to keep it consistent throughout. Maybe adding these terms to your Figure 1 would also be helpful for clarifying purposes. 3. Given that you are interested in more than just the impact of PGHD, I am curious as to why you would limit your inclusion to those articles reporting outcomes. There may be valuable literature on, for example, the processes of generating PGHD that would not include outcomes. You may want to discuss this criterion for inclusion at greater length to link it to your objectives. 4. In Table 2, I would recommend only providing the exclusion criteria, as the two columns are duplicative and the exclusion criteria are more explicitly defined. For the first criterion, I would describe this in greater detail, so that it is clear what is meant (this links to comment #2, above). 5. There are minor grammatical issues (e.g., page 19 lines 8-22) where the meaning of the sentence is somewhat obscured by the phrasing. 6. In Step 6: Consultation, it would seems that the stakeholders

	should also have been included in the protocol development, but it isn't clear if this happened. What consultation happened during protocol development? 7. More discussion of other synthesis efforts in this area might be helpful to help contextualize the current work.

REVIEWER	Martin Entwistle Ares Health Systems, USA
REVIEW RETURNED	30-Jan-2018

GENERAL COMMENTS	Overall this paper and its objectives have merit. The authors correctly identify that an understanding of what works in the use of PGHD for prevention and health promotion is hampered by lack of consistency in approach to research and evaluation and an analysis of the literature, as proposed, could be of significant assistance to knowledge in this area. The paper has a significant framing issue in that the authors have chosen to limit the review to the use of PGHD for prevention and health promotion and argued that the inclusion of use of PGHD for other purposes, eg management of existing conditions should be excluded as it would make the scope of the review too large. This narrowing of scope concerns me however after reflection I think the narrowing of scope is valid, however this framing must be spelled out in the abstract so that this limitation is clear to any reader. At this point it is not. The Strengths and Limitations section should be updated to reflect the impact of the scoping and framing selected by the authors. If the financial, technical, practical and ethical perspectives are excluded from the analysis, these need to be called out as significant limitations to the study. I do not see funding or conflict of interest statements. There are a number of typos and grammatical errors through the paper that need to be corrected as well as checking the citations. For example I can see a number of references that are mis-cited; see page 6 line 45 citation #17 should be #20 or possibly #21. I would like to see the arguments for Study Rationale and the Study Objectives expanded upon and spelled out in more detail so that the value of this study becomes clearer. Per the cited methodological approach "Linking a clear purpose for undertaking a scoping study to a well-defined research question at the first stage of the framework will help to provide a clear rationale for completing the study and facilitate decision making about study selection and data extraction later in the methodological process". These sections correctly outline that the literature is fragmented in approach, but how the proposed research will do to address this challenge could be better defined, eg "we hypothesise that a formalised analysis and review of the literature in this area can provide an interpretation of where there is agreement on successful approaches to the use of PGHD as well as identifying areas that require further research to identify how improvements can be made. Page 6 Lines 34 - 36. It is unclear whether the PGHD-related challenges of a financial, technical, practical and ethical nature are included or excluded from the prosed review. I believe it is important they are included. For example the availability collection and use of

	PGHD is markedly impacted by such financial issues as to the availability of devices to collect the data, and payment models for collection and use. Uncomfortable though these issues may be, they materially impact the proposed research question, and should be included. Page 8 lines 11 - 14 state the objectives as … existing knowledge on the generation, share, utilization, context and impact of electronic patient generate health data. This repeats a common scoping statement to use of PGHD as stated in the literature, however this is a somewhat abstract view an misses a number of dimensions which are key to availability and use of PGHD and represent significant barrier if now addressed. It would be remis of the review to omit these. The scoping could be better frames as follows; … the generation, collection, communication, sharing, interpretation, utilization, context and impact……. [This modified statement would need to be repeated at other relevant points in the paper, eg page 13 lines 33 - 39. Page 11 Line 21. I would strongly urge further changes to this diagram this is not accurately representative of the current flows for collection and use of PGHD for prevention and health promotion. It describes a medical model with all data passing through a healthcare context and healthcare provider before returning to the patient. Further advice may need to be sought to modify the diagram to accurately represent the broader flows of PGHD for prevention and health promotion. For example, there are many apps that provide support for prevention and health promotion that do not involve the healthcare context. The patient contributes PGHD and gets feedback on actions to take to address prevention and health promotion. This model may be criticisable, but it is already in extensive use. Similarly there are wellness providers, including for example weight management programs conducted completely outside the healthcare context. These should be represented in the diagram. Page 11 lines 28 - 31. The authors are proposing a more comprehensive definition to PGHD. This paragraph would be improved if rather that stating …In addition to the definition given in…, the new more comprehensive definition be proposed in full and explicitly stated. Page 12 line 24. wellness providers and others involved in behavior change eg health coaches should be included in this list of professionals. Page 12 line 43. I disagree that inpatient and hospital contexts should be excluded. The scope of the review has already been limited to prevention and health promotion. It is an unsafe assumption that inpatient and hospital settings are not involved in disease prevention and health promotion and therefore exclude research with these settings are their context from the proposed review. There may be valuable insights gained from their inclusion. Page 14 line 10. What is the rationale for selecting a 15 year scope for review. This should be explained. Page 14 line 53. What are the proposed qualifications and roles of the two members of the research team conducting this work? How will the individuals be selected? These dimensions should be explicit

	in the methods as they critically impact the results achieved. Page 15 Line 49. What are the proposed qualifications and roles of the third reviewer? How will the individual be selected? These dimensions should be explicit in the methods and summarised in the abstract as they critically impact the results achieved. Page 14 Lines 32 - 55. Further explanation of this iterative review process is required. The method by which a final outcome is achieved is not explicit. For example, for disputed papers, must consensus be achieved for inclusion? Does the third reviewer have a arbitration role, ie acts with a casting vote to make a final determination of whether results are included in the analysis or not Page 17 Line 47. Is the senior investigator of the team the same individual as the third reviewer. Once again the qualifications, role and selection process of this individual should be spelled out as they are key to the methodological approach. Mention of this role should appear in the abstract Page 19 Lines 49 - 53. Reference to GRADE and PRISMA appears repetitive of statements made on page 13 lines 11 - 15. One way to avoid this is to make reference here to the recommended use of GADE and PRISMA in the methodological framework previously identified [#37, #38]

VERSION 1 – AUTHOR RESPONSE

Comments by Isomi Miake-Lye (Reviewer 1) and Author Replies:

Reviewer 1 Initial Statement: The rapidly growing area of electronic patient-generated health data provides both opportunities and challenges for the authors of this protocol. There is great potential for scientific contribution from this scoping review. The most serious concern this raises is whether the large amount of published information I anticipate the team will find will be amenable to the protocol described. While such a large and detailed review would be valuable, is it feasible? Has the team run preliminary searches that might indicate the magnitude of evidence they are expecting to synthesize? Aside from this overarching concern, a few more specific suggestions are below:

Reply: Thank you very much for taking the time to revise our manuscript and for all your valuable remarks. We very much appreciate your recognition of our review's scientific potential. Your concern regarding the amount of evidence is very legitimate and reflects our considerations when planning and drafting this protocol. We have indeed conducted a few preliminary examinations of the literature, which indicated a relatively vast amount of published studies. However, considering those preliminary searches, we believe that the review's restricted scope on prevention and health promotion, as well as our inclusion criteria (e.g. describing some patient and provider involvement) will limit the final number of eligible studies to 250 at most, which would fall within our capacities and time-frame.

Reviewer 1 Comment 1: In the title it would be more accurate to call this a scoping review protocol, rather than a systematic scoping review protocol.

Reply: Thank you for that remark. Our initial thought for adding the term "systematic" aimed to underline the systematic and comprehensive methodological basis of this scoping study – nonetheless, we agree that is indeed more accurate to leave it out. We have adjusted the title accordingly to "Electronic Patient-Generated Health Data to Facilitate Prevention and Health

Promotion: A Scoping Review Protocol" (p.1)

Reviewer 1 Comment 2: There is some wording clarification that would be helpful for the language that repeats related to the study objectives: "generation, share, utilization, context and impact" appears a few times. I suggest each of these being its own question to help bring clarity to this phrase. I currently am not sure what each means, which may be influencing some of my later suggestions. In addition, the phrasing in the abstract is different than how it appears in the manuscript, so once a phrasing is chosen, it would be helpful to keep it consistent throughout. Maybe adding these terms to your Figure 1 would also be helpful for clarifying purposes.

Reply: Thanks a lot for this comment – it helped us clarifying those concepts, which we believe makes the protocol much more understandable to the readers. We have therefore added a table under the section "Conceptual Model and Definitions" that outlines those dimensions individually and attaches them to a corresponding question and hypothetical examples. Kindly find the new table (table 2) on p. 11-12.

The table includes three additional terms that have been correctly suggested by the second reviewer. Those are "collection", "communication" and "interpretation". We have changed the phrasing in the abstract, as well as the entire document to reflect those changes and ensure consistency. As correctly suggested, we have added those terms in our revised framework (figure 1) to make sure the reader understands where each of these dimensions is predominantly positioned within the flow of PGHD. Please find all changed passages below:

p. 9-10 "Our adapted version, provided in figure 1, retains the same flow, but additionally emphasizes the use of PGHD for fostering or providing disease prevention, health promotion and patient-provider or patient-technology interactions. The framework visualizes the generation of different health data types by patients, as well as their collection, sharing, communication and use."

p. 2 Abstract: "Ethics and Dissemination: The scoping review described in this protocol aims to establish a baseline understanding of electronic PGHD generation, collection, communication, sharing, interpretation, utilization, context and impact for preventive purposes."

p. 7 Study Objectives: "The overarching objective of the described study is to identify, map and synthesize existing knowledge on the generation, collection, communication, sharing, interpretation, utilization, context and impact of electronic PGHD for the facilitation and provision of prevention and health promotion."

p.13 Identifying the research question: "…the review's primary, overarching research question is defined as: "What is our knowledge status, retrieved from existing literature, on the generation, collection, communication, sharing, interpretation, utilization, context and impact of electronic PGHD for the facilitation of patient/consumer-centered preventive activities and health promotion?"."

p. 16 Table 3: "Does not address generation, collection, communication, sharing, interpretation, utilization, context or impact of electronic PGHD"

Reviewer 1 Comment 3: Given that you are interested in more than just the impact of PGHD, I am curious as to why you would limit your inclusion to those articles reporting outcomes. There may be valuable literature on, for example, the processes of generating PGHD that would not include outcomes. You may want to discuss this criterion for inclusion at greater length to link it to your objectives.

Reply: We apologize, as the wording we had previously chosen might indeed have been prone to

misunderstandings. With "…not addressing any prevention and health promotion outcomes, will lead to exclusion" we meant that we will exclude articles that focus on patient or provider attitudes/opinions about a PGHD, only if they are not placed in a clear context of prevention and health promotion (e.g. cancer patient attitudes on the use of a patient-data transmitting m-health intervention for coping with chemotherapy symptoms [hypothetical]). Indeed, it is not necessary for an article to be of evaluative nature (include outcomes) in order to be included. We have changed the wording to make this clear.

p. 15 Study Selection: "The absence of elements or indicators referring to prevention and health promotion (e.g. reduction of blood pressure) or a shallow exploration of patient or provider attitudes towards PGHD and PGHD-based tools, without being clearly defined within a prevention or health promotion context, will lead to exclusion."

Reviewer 1 Comment 4: In Table 2, I would recommend only providing the exclusion criteria, as the two columns are duplicative and the exclusion criteria are more explicitly defined. For the first criterion, I would describe this in greater detail, so that it is clear what is meant (this links to comment #2, above).

Reply: We very much agree with that remark and have modified the table. The new table (p. 16), now table 3 due to addition of a new table before, includes one column, with the exclusion criteria and has been renamed to "Table 3. Exclusion Criteria". As described in our reply to the previous comment, the elements of criterion 1 are now outlined in table 2 (p. 11-12), for which we decided to not repeatedly expand the definitions here to avoid any redundancies. However, we refer the reader back to table 2.

p. 16
Table 3 Exclusion Criteria
1. Does not address the generation, collection, communication, sharing, interpretation, utilization, context or impact of electronic PGHD (as outlined in Table 2)
2. Lacks a focus on prevention and health promotion (e.g. exclusively addresses rehabilitation or therapeutic interventions)
3. Addresses patient-generated information that is not personal health-related
4. Does not describe, explore and analyse some form of patient and provider involvement
5. Does not address or include adults
6. Written in a language other than English or German

Reviewer 1 Comment 5: There are minor grammatical issues (e.g., page 19 lines 8-22) where the meaning of the sentence is somewhat obscured by the phrasing.

Reply: Thanks a lot for pointing on this. We tried to increase the clarity of that paragraph and ensure that its message is not obscured by: (a) doing some rephrasing, (b) shortening some unnecessarily long sentences and (c) re-ordering a few sentence elements. We have also had an external person carefully proofread the entire manuscript and correct any orthographic or syntactic errors. We have corrected any mistakes throughout the protocol with the track change function (as we did for all other revisions).

p. 20 "The described review constitutes the first step of a larger research project on digital solutions for disease prevention and health promotion. Its results ultimately fulfill the function of establishing a comprehensive conceptual knowledge of electronic PGHD and will be used to inform prospective research steps. Initiation of screening and data collection is planned for February 2018. Findings will be disseminated at relevant conferences and symposia. Results will be published and additionally shared with our provider and patient-partners and their networks, as well as local and national organizations operating in the field of digital health. As our methodology is based on the review of publicly available information, ethical approval is not required. Any amendments to this protocol will

be documented precisely and listed in the final review publication."

Reviewer 1 Comment 6: In Step 6: Consultation, it would seems that the stakeholders should also have been included in the protocol development, but it isn't clear if this happened. What consultation happened during protocol development?

Reply: Thanks a lot for requesting a clarification on that step, as it is an important one. Levac et al. [41] describe that step as optional, however, very valuable for methodological rigor and result validity. They additionally outline that it remains unclear at what stages stakeholder involvement would be ideal, suggesting that there might indeed be no single "golden standard". They continue on highlighting the value of stakeholder involvement at rather "later" study stages, such as after preliminary findings have been retrieved, underlining the importance of that step for knowledge transfer. We certainly see the value of involving patients and providers at the very early stage of protocol development, however, could not achieve that due to practical limitations and time constraints. External input during protocol development is focused on expert feedback, kindly provided by Prof. Deborah Cohen (US) (acknowledged on p. 20), She provided conceptual feedback during early stages of the protocol, feedback on the search strategy as well as feedback on the final versions of the manuscript. We have adjusted step. 6 to reflect that

p. 19-20 "Levac et al., pointed out that consultation, the sixth, transversal optional stage of the scoping studies framework, may enable stakeholder engagement and provide valuable input, beyond the information provided in the literature.[41] As already described throughout the protocol, expert consultation is central at all stages of this study. An external expert in the area of PGHD has been consulted twice during the development of this protocol, providing conceptual and content-related feedback and advice. During the review process, we will additionally establish regular consultation with one provider-partner and at least one patient-partner. Both stakeholders will be asked to provide feedback during data extraction, appraisal of preliminary results, data synthesis and interpretation. Finally, we aim to engage digital health experts within the team's own institution for additional advice. All involved experts and stakeholders will be acknowledged in the final publication."

Reviewer 1 Comment 7: More discussion of other synthesis efforts in this area might be helpful to help contextualize the current work.

Reply: Very good point. We have added a paragraph (p. 7) with a few additional and notable reviews in the field, complemented by a sentence on how our review is positioned in relation to existing syntheses.

p. 7 Study Rationale: "Further research syntheses outline the impacts of PGHD-linked tools, such as wearables and self-tracking devices, on specific risk factors and conditions. For example, Gierisch et al. summarized the effects of wearable sensing technologies on physical activity, Fu et al. reviewed the impact of mobile applications, including electronic monitoring and data transmission, on blood glucose levels, while Fletscher et al. explored the effects of blood pressure monitoring on health behaviors.[32-34] Existing reviews tend to focus on specific forms of PGHD and specific risk factors or conditions, often with reference to disease management. Our proposed review aims to depart from that "focused" approach to holistically address electronic PGHD and their use in preventive and health promoting activities. We hypothesize that approaching the literature with a broader lens and not limiting our focus to a specific PGHD format will ultimately enable a holistic understanding of where and how successfully PGHD are currently used. Finally, our analysis, being equally encompassing, may provide insights into how electronic PGHD are applied, adding to our knowledge on the contexts of PGHD utilization and how those might contribute to improvements and success."

Comments by Martin Entwistle (Reviewer 2) and Author Replies:

Reviewer 2 Initial Statement: Overall this paper and its objectives have merit. The authors correctly identify that an understanding of what works in the use of PGHD for prevention and health promotion is hampered by lack of consistency in approach to research and evaluation and an analysis of the literature, as proposed, could be of significant assistance to knowledge in this area.

Reply: Thank you very much for taking the time to revise our manuscript. All your comments and remarks have been very valuable and of a great help for revising our protocol to the better. We are glad that you share our view on the current state of PGHD literature with regards to prevention and health promotion and appreciate your recognition of our study's merit in adding knowledge and value in this area.

Reviewer 2 Comment 1: The paper has a significant framing issue in that the authors have chosen to limit the review to the use of PGHD for prevention and health promotion and argued that the inclusion of use of PGHD for other purposes, eg management of existing conditions should be excluded as it would make the scope of the review too large. This narrowing of scope concerns me however after reflection I think the narrowing of scope is valid, however this framing must be spelled out in the abstract so that this limitation is clear to any reader. At this point it is not.

Reply: Thank you very much for this comment. It accurately reflects our initial thoughts and discussions when drafting this review's research question and framing its scope. Our justification for that framing goes beyond the importance of prevention and health promotion as such, and is based upon the findings of a few preliminary searches, suggesting lacking research syntheses on prevention and health promotion in relation to electronic PGHD. Nonetheless, we fully acknowledge that this is one of the paper's limitations. We very much appreciate that you perceive that scope as valid and have adjusted the abstract, as well as strengths and limitations section of the manuscript to make that limitation clear to the readers.

p. 2 We made our scope clear in the abstract: "We will include literature with a focus on electronic PGHD and linked to prevention and health promotion. Literature on tertiary prevention, driven by existing discomfort or disability, goes beyond the review's scope and will be excluded."

p. 3 We made the limitation clear in the strengths and limitation section: "As the review's scope is restricted to disease prevention and health promotion, the resulting typology of electronic PGHD as well as the overall findings might not be applicable beyond those domains"

Reviewer 2 Comment 2: The Strengths and Limitations section should be updated to reflect the impact of the scoping and framing selected by the authors. If the financial, technical, practical and ethical perspectives are excluded from the analysis, these need to be called out as significant limitations to the study.

Reply: Thanks for pointing out the importance of updating our strengths and limitation section. As we also outline in greater detail in our response to your first comment, we have adjusted the section to clearly reflect the limitation of our framing. We have copied the changed section in our reply to your previous comment, and also a second time below.

p. 3 "As the review's scope is restricted to disease prevention and health promotion, the resulting typology of electronic PGHD as well as the overall findings might not be applicable beyond those domains "

In addition, we clarify in our response to a latter comment of yours, that we will synthesize financial, technical, practical and ethical challenges. Thus, we did not include that as a limitation. However, we

have adjusted the manuscript to make clear that those dimensions will be considered.

p. 9 “Whenever available, we aim to additionally synthesize PGHD-related challenges, such as of financial, technical, practical and ethical nature.”

Reviewer 2 Comment 3: I do not see funding or conflict of interest statements.

Reply: Please find those two statements on p. 20

“Funding statement: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors. The first author’s salary is funded by the Béatrice Ederer-Weber Fellowship.
Competing interests statement. We have read and understood the BMJ policy on the declaration of interests and declare that we have no competing interests.”

Reviewer 2 Comment 4: There are a number of typos and grammatical errors through the paper that need to be corrected as well as checking the citations. For example I can see a number of references that are mis-cited; see page 6 line 45 citation #17 should be #20 or possibly #21.

Reply: Thanks a lot for this comment. We have had an external person to carefully proofread the entire manuscript and correct any orthographic or syntactic errors. We have corrected any mistakes throughout the protocol with the track change function (as we did for all other revisions).

Regarding reference 17, you are absolutely right that this statement is also provided by reference 20. We initially decided to only cite 17 in that sentence, as the white paper by Shapiro et al [17] has coined that definition and was published before the factsheet [20]. However, acknowledging that both might be cited here, we added reference 20 [now reference 18] in addition to 17. We corrected the numbering in the reference list and throughout the manuscript accordingly.

p. 5 “The phenomenon of electronic patient-generated health data (PGHD) can be positioned on the intersection between the digital revolution and the patient-centered care movement. A landmark whitepaper by the US Office of the National Coordinator for Health Information Technology defines PGHD as “health-related data—including health history, symptoms, biometric data, treatment history, lifestyle choices, and other information—created, recorded, gathered, or inferred by or from patients or their designees (i.e., care partners or those who assist them) to help address a health concern”.[17, 18] Electronically captured, shared and utilized PGHD consists of digitally rooted information that is created outside traditional healthcare contexts.[17, 18]”

We also went through each in-text citation individually and double checked that all are cited correctly. We conducted the following changes:

a) Reference 31 [now reference 28] was previously cited wrongly on p. 7. We corrected that, shifted the citation to p. 6 and switched its number from 31 to 28. We subsequently corrected the numbers in the reference list and throughout the manuscript. Please find the corrected citation on p. 6:
“Furthermore, PGHD can add comprehensiveness to the assessment of an individual’s health status by narrowing information gaps, enhancing patient-provider interaction and reducing data errors.[25-28]”

b) We added three new references as a response to a previous comment by reviewer 1. Those took up the numbers 32, 33, 34 (p. 7). We subsequently corrected the numbers in the reference list and throughout the manuscript. Please find the new citations on p. 7: “For example, Gierisch et al. summarized the effects of wearable sensing technologies on physical activity, Fu et al. reviewed the

impact of mobile applications, including electronic monitoring and data transmission, on blood glucose levels, while Fletscher et al. explored the effects of blood pressure monitoring on health behaviors.[32-34]”

Reviewer 2 Comment 5: I would like to see the arguments for Study Rationale and the Study Objectives expanded upon and spelled out in more detail so that the value of this study becomes clearer. Per the cited methodological approach "Linking a clear purpose for undertaking a scoping study to a well-defined research question at the first stage of the framework will help to provide a clear rationale for completing the study and facilitate decision making about study selection and data extraction later in the methodological process". These sections correctly outline that the literature is fragmented in approach, but how the proposed research will do to address this challenge could be better defined, eg "we hypothesise that a formalised analysis and review of the literature in this area can provide an interpretation of where there is agreement on successful approaches to the use of PGHD as well as identifying areas that require further research to identify how improvements can be made.

Reply: Thanks a lot for this valuable comment. We fully agree that a clear and understandable purpose is crucial for all upcoming stages, as well as for the readers perception of the study’s added value. Following your recommendation, as well as a previous recommendation by Reviewer 1 [on more discussion on existing synthesis efforts] we have:

a) Expanded the study rationale paragraph with a few notable existing reviews in the field, highlighting how our study distinguishes from existing synthesis

p. 7: "Further research syntheses outline the impacts of PGHD-linked tools, such as wearables and self-tracking devices, on specific risk factors and conditions. For example, Gierisch et al. summarized the effects of wearable sensing technologies on physical activity, Fu et al. reviewed the impact of mobile applications, including electronic monitoring and data transmission, on blood glucose levels, while Fletscher et al. explored the effects of blood pressure monitoring on health behaviors.[32-34] Existing reviews tend to focus on specific forms of PGHD and specific risk factors or conditions, often with reference to disease management. Our proposed review aims to depart from that “focused” approach to holistically address electronic PGHD and their use in preventive and health promoting activities.”

b) We adjusted the last paragraph of the study rationale section, spelling out of how our review’s comprehensive lens & analysis will ultimately address the outlined fragmentation in the literature, as very well and correctly articulated by you.

p. 7 “We hypothesize that approaching the literature with a broader lens and not limiting our focus to a specific PGHD format will ultimately enable a holistic understanding of where and how successfully PGHD are currently used. Finally, our analysis, being equally encompassing, may provide insights into how electronic PGHD are applied, adding to our knowledge on the contexts of PGHD utilization and how those might contribute to improvements and success”

c) We finally slightly reworded the last sentence of the patient objectives paragraph to emphasize the aim of aim of identifying with further research needs

p. 9: “Finally, inherent to our overall aim of mapping and synthesizing existing knowledge, we expect to draw final conclusions on current research trends, as well as identify areas with further research needs.”

Reviewer 2 Comment 6: Page 6 Lines 34 - 36. It is unclear whether the PGHD-related challenges of a

financial, technical, practical and ethical nature are included or excluded from the prosed review. I believe it is important they are included. For example the availability collection and use of PGHD is markedly impacted by such financial issues as to the availability of devices to collect the data, and payment models for collection and use. Uncomfortable though these issues may be, they materially impact the proposed research question, and should be included.

Reply: Thank you for this remark. The starting of this sentence ["Without disregarding significant PGHD-related challenges, evidence suggests…" p. 6] is indeed prone to misunderstandings. With this sentence we merely aimed to state that despite those challenges, PGHD are very promising and hold potential value. We therefore changed the sentence to:

p. 6: "Despite significant PGHD-related challenges, evidence suggests that digitally enabled PGHD utilization can facilitate both prevention and patient engagement, ultimately reducing unnecessary costs and inefficiencies.[12, 13, 17, 24-26]"

We fully agree that it is important to capture those PGHD related challenges (financial, technical, practical and ethical), as they are crucial to all aspects of PGHD use. We do not indent to exclude those challenges from our synthesis but acknowledge that it might not have been very explicit in the previous protocol version, as we merely summarized them with the term "Barriers". To make that clear, we added a sentence in the study objectives paragraph, where we state that we will synthesize those challenges. We deleted the part of 'financial, technical, practical and ethical nature' in the previous sentence (p.6) above to avoid repetitions.

p. 9 Study Objectives: "Whenever available, we aim to additionally synthesize PGHD-related challenges, such as of financial, technical, practical and ethical nature."

Reviewer 2 Comment 7: Page 8 lines 11 - 14 state the objectives as … existing knowledge on the generation, share, utilization, context and impact of electronic patient generate health data. This repeats a common scoping statement to use of PGHD as stated in the literature, however this is a somewhat abstract view an misses a number of dimensions which are key to availability and use of PGHD and represent significant barrier if now addressed. It would be remis of the review to omit these. The scoping could be better frames as follows; … the generation, collection, communication, sharing, interpretation, utilization, context and impact……. [This modified statement would need to be repeated at other relevant points in the paper, eg page 13 lines 33 - 39.

Reply: Your suggested additions [collection, communication, interpretation] and new phrasing is indeed very helpful for capturing of all those dimensions that are crucial when addressing PGHD. We agree that the ways data are collected, communicated and finally interpreted should and cannot be ignored. We have therefore adapted the framing of that objective, which is now stated as:

p. 8 Table 1: " Overarching Objective: Identify, map and synthesize existing knowledge on the generation, collection, communication, sharing, interpretation, utilization, context and impact of electronic patient generated health data (PGHD) for the facilitation and/or provision of preventive activities and health promotion"

This framing has been used throughput the manuscript, such as:

p. 2 Abstract: "The scoping review described in this protocol aims to establish a baseline understanding of electronic PGHD generation, collection, communication, sharing, interpretation, utilization, context and impact for preventive purposes."

p. 9-10 "Our adapted version, provided in figure 1, retains the same flow, but additionally emphasizes

the use of PGHD for fostering or providing disease prevention, health promotion and patient-provider or patient-technology interactions. The framework visualizes the generation of different health data types by patients, as well as their collection, sharing, communication and use."

p. 7 Study Objectives: "The overarching objective of the described study is to identify, map and synthesize existing knowledge on the generation, collection, communication, sharing, interpretation, utilization, context and impact of electronic PGHD for the facilitation and provision of prevention and health promotion."

p.13 Identifying the research question: "…the review's primary, overarching research question is defined as: "What is our knowledge status, retrieved from existing literature, on the generation, collection, communication, sharing, interpretation, utilization, context and impact of electronic PGHD for the facilitation of patient/consumer-centered preventive activities and health promotion?"."

p. 16 Table 3: "Does not address generation, collection, communication, sharing, interpretation, utilization, context or impact of electronic PGHD"

Finally, in response to a comment by reviewer 1, we have also created a new table (Table 2, p. 11-12) which outlines all those dimensions and attaches them to hypothetical examples.

Reviewer 2 Comment 8: Page 11 Line 21. I would strongly urge further changes to this diagram this is not accurately representative of the current flows for collection and use of PGHD for prevention and health promotion. It describes a medical model with all data passing through a healthcare context and healthcare provider before returning to the patient. Further advice may need to be sought to modify the diagram to accurately represent the broader flows of PGHD for prevention and health promotion. For example, there are many apps that provide support for prevention and health promotion that do not involve the healthcare context. The patient contributes PGHD and gets feedback on actions to take to address prevention and health promotion. This model may be criticisable, but it is already in extensive use. Similarly there are wellness providers, including for example weight management programs conducted completely outside the healthcare context. These should be represented in the diagram.

Reply: We very much appreciate this comment. We agree that electronic PGHD are not restricted within the traditional medical context and acknowledge that the previous framework failed to capture that broadness. We have therefore revised the framework and undertook the following changes (please see file 1):

a) Deleted the element depicting an exclusive focus on healthcare context and healthcare provider. We additionally deleted "healthcare" in front of provider throughout the manuscript and table 3 (p. 16) to bring that in line with adjusted framework

b) Exchanged that element with the term "intermediary" and added examples, including wellness providers, technologies and "others" to leave some space for new additions by the review's findings

c) As suggested be reviewer 1, we have added the addressed dimensions (generation, collection, sharing, communication, utilization, interpretation…) into the framework. We restructured the framework to facilitate those changes in a way that is understandable to the reader.

d) As the framework has been opened up beyond the "medical context" we added the term "Patient-Technology Interaction" next to Patient-Provider interaction, for those cases, where the intermediary between PGHD and prevention/health promotion is an automated program. We also added patient-technology interaction next to patient-provider interaction throughout the manuscript (e.g. p. 8

“Interaction: Identify and synthesize existing data that links the utilization of electronic PGHD to patient-provider or patient-technology interaction”)

e) We changed the paragraph that introduces the framework, as well as the figure legend accordingly to reflect those modifications

p. 9-10 “In order to guide and structure the scoping review process, we have adapted and utilized a conceptual framework that was prepared for the US office of the National Coordinator for Health Information Technology and reported in a 2012 White Paper.[17] The original framework visualizes the flow and context of PGHD, emphasizing on data capture, transfer and review.[17] Our adapted version, provided in figure 1, retains the same flow, but additionally emphasizes the use of PGHD for fostering or providing disease prevention, health promotion and patient-provider or patient-technology interactions. The framework visualizes the generation of different health data types by patients, as well as their collection, sharing, communication and use.”

p. 24: Figure Legend: “Figure 1: Adapted Framework for Patient-Generated Health Data (PGHD) Flow and Context for Prevention and Health Promotion.[17]. The Framework visualizes the flow of PGHD from the patient/consumer (generation & collection stages), passing through intermediaries (communication, sharing, interpretation stages) and back to the patient in form of prevention, health promotion and interaction (utilization & impact stages).”

Reviewer 2 Comment 9: Page 11 lines 28 - 31. The authors are proposing a more comprehensive definition to PGHD. This paragraph would be improved if rather that stating …In addition to the definition given in…, the new more comprehensive definition be proposed in full and explicitly stated.

Reply: Great point. It is certainly easier for the reader to follow when stating the full definition again. Thus, we state the entire new definition, including (a) the part coined by the white paper [17], (b) the digital element, (c) the distinction from PROs and (d) the importance of patient control.

p. 10 “For the purposes of this study, we propose a more comprehensive definition of electronic PGHD. Accordingly, the term emphasizes digitally rooted “health-related data- including health history, symptoms, biometric data, treatment history, lifestyle choices, and other information—created, recorded, gathered, or inferred by or from patients or their designees (i.e., care partners or those who assist them) to help address a health concern”, captured outside traditional healthcare contexts and being distinct from other forms of patient-provided data, such as patient-reported outcomes (PROs).[17, 36] PROs are commonly informed, standardized and driven by healthcare providers, lacking the level of patient control that is characteristic for PGHD.[17, 36] Thus, responsibility for capturing, recording and sharing electronic PGHD lies with the patients.[17]”

Reviewer 2 Comment 10: Page 12 line 24. wellness providers and others involved in behavior change eg. health coaches should be included in this list of professionals.

Reply: We totally agree with that suggestion. We have therefore deleted the term “healthcare” in front of “provider” throughout the paper, to avoid confusion that we will exclusively focus on traditional healthcare contexts (doctor-patient). That change is also in line with the adjustments that we have made on our framework, following one of your others comments (replied in detailed above). We have adjusted our definition of provider accordingly:

p. 11 “The term provider is defined as any professional that is responsible for offering health-related services, including health behavior and lifestyle changes (e.g. primary care physicians, primary care nurses, pharmacists, specialist physicians, physiotherapists, psychologists, wellness providers, health and lifestyle coaches).”

Reviewer 2 Comment 11: Page 12 line 43. I disagree that inpatient and hospital contexts should be excluded. The scope of the review has already been limited to prevention and health promotion. It is an unsafe assumption that inpatient and hospital settings are not involved in disease prevention and health promotion and therefore exclude research with these settings are their context from the proposed review. There may be valuable insights gained from their inclusion.

Reply: Thanks a lot for this comment. It offers a perception that we admittedly did not fully embrace when preparing this protocol. Our restriction was merely based on the assumption that existing hospital-based and inpatient-focused studies might predominantly have a therapeutic/curative focus, which would fall beyond of our scope. However, we fully acknowledge that this assumption is not safe and have agreed to not automatically exclude hospital and inpatient-studies. That change did not require any modifications to our search strategy as we had not restricted our keywords to inpatient settings. However, we have omitted that sentence from the manuscript

Deleted Section: “Studies taking place within inpatient & hospital contexts will fall out of the review’s scope, considering that disease prevention and health promotion is not a priority activity in such settings. For coherence purposes, the word ‘patient’ is used interchangeably for healthcare consumer, without necessarily denoting the presence of a disease”

Reviewer 2 Comment 12: Page 14 line 10. What is the rationale for selecting a 15 year scope for review. This should be explained.

Reply: Thank you for asking for a justification on the period. We have added it in the manuscript.

p. 13 “Our strategy is purposively sensitive, entailing a variety of keywords related to PGHD, restricted to adult populations and research published in the last 15 years. Limiting our research to the last 15 years is based on our preliminary searches, that indicate an emergence and accumulation of relevant literature during the last decade. We purposively added another five years to ensure that we capture all valuable literature and trends.”

Reviewer 2 Comment 13: Page 14 line 53. What are the proposed qualifications and roles of the two members of the research team conducting this work? How will the individuals be selected? These dimensions should be explicit in the methods as they critically impact the results achieved.

Reply: It is absolutely right that these dimensions are critical for the conduction and results of the review. We therefore added those:

p. 14 “The first author of this protocol, having previous experience with literature reviews and an educational background in digital health interventions for disease prevention purposes, will take the first reviewer role. The second reviewer will be recruited based on substantial experience in planning and conducting literature reviews, an educational background in a health-related discipline and a good understanding of the proposed topic, preferably with previous work experience in a PGHD-related topic. Both will be responsible for independently completing the screening, selection and data extraction process, with the first reviewer having the added responsibility of data synthesis and final manuscript preparation.”

Reviewer 2 Comment 14: Page 15 Line 49. What are the proposed qualifications and roles of the third reviewer? How will the individual be selected? These dimensions should be explicit in the methods and summarized in the abstract as they critically impact the results achieved.

Reply: The third reviewer, entering the process whenever conflicts remain will be one of senior

research team members, Dr. Margot Mütsch or Prof. Dr. Milo Puhan (Initials added in the manuscript). We have added their qualifications and clarified their role. We have also added a sentence in the abstract to reflect that.

p. 2 Abstract: “Two independent reviewers will complete study selection and data extraction. One of the team’s senior research members will act as a third reviewer and make the final decision over disputed documents.”

P. 15-16 “All discordant articles will be reexamined and persisting disputes will be resolved through consultation with a third reviewer, selected among one of the senior members of the research team (MM, MP) and being responsible for the final decision on disputed papers. Both are members of Cochrane Public Health Europe and have considerable thematic and methodological knowledge”

Reviewer 2 Comment 15: Page 14 Lines 32 - 55. Further explanation of this iterative review process is required. The method by which a final outcome is achieved is not explicit. For example, for disputed papers, must consensus be achieved for inclusion? Does the third reviewer have a arbitration role, ie acts with a casting vote to make a final determination of whether results are included in the analysis or not

Reply: Thanks a lot for the remark. We have revised the paragraph to make the process clearer to the reader. We undertook the following changes:

a) Clarified the process of calculating interrater agreement and the rationale behind it

b) Added that a consensus is required in order to enter full-text screening. Our initial approach required that any study that was deemed as potentially eligible by at least one reviewer would enter full-text screening. Considering the topics complexity and high number of retrieved documents, we have revised that to resolving conflicts and achieving consensus before an article enters full-text review

c) We outline when and why consultation will follow and the process will be repeated

d) As very well suggested in the comment, we clarified the final selection process, in which one senior research team members will decide on eligibility of disputed papers

p. 15-16 “We will assess inter-rater agreement during both phases, using Cohen’s k coefficient.[43] The coefficient, calculated after screening the first 50 titles and abstracts, will act as an indicator of whether both reviewers understand and apply the inclusion criteria in an equal, correct and coherent manner. Low agreement (<0.40) will be followed by a consultation of the two reviewers, and if needed, adjustment or rewording of the eligibility criteria. This process will be repeated for the next 50 titles and abstracts and until interrater agreement reaches substantial levels (>0.40). After the title and abstract screening is completed, the two reviewers will meet to compare their results. Consulting the inclusion and exclusion criteria, they will try to resolve conflicts and reach consensus on eligibility for full-text review. Studies that are unclear and do not allow for consensus will also enter full-text screening. During full-text review, which will be independently completed by the same two reviewers, interrater agreement will be calculated for the first 15 studies. After completion of full-text screening, reviewers will meet again to compare their results. All discordant articles will be reexamined and persisting disputes will be resolved through consultation with a third reviewer, selected among one of the senior members of the research team (MM, MP) and being responsible for the final decision on disputed papers. Both are members of Cochrane Public Health Europe and have considerable thematic and methodological knowledge.”

Reviewer 2 Comment 16: Page 17 Line 47. Is the senior investigator of the team the same individual as the third reviewer. Once again the qualifications, role and selection process of this individual should be spelled out as they are key to the methodological approach. Mention of this role should appear in the abstract

Reply: We totally agree that the qualifications and roles of all reviewers are crucial for the study's methodology. As outlined in the response to one of the previous comments, the third reviewer will be one of the team's senior research members (MM, MP). We adjusted the manuscript to make that clear and added that in the abstract.

p. 2 Abstract: "One of the team's senior research members will act as a third reviewer and make the final decision over disputed documents"

p. 16 "All discordant articles will be reexamined and persisting disputes will be resolved through consultation with a third reviewer, selected among one of the senior members of the research team (MM, MP) and being responsible for the final decision on disputed papers. Both are members of Cochrane Public Health Europe and have considerable thematic and methodological knowledge"

Reviewer 2 Comment 17: Page 19 Lines 49 - 53. Reference to GRADE and PRISMA appears repetitive of statements made on page 13 lines 11 - 15. One way to avoid this is to make reference here to the recommended use of GADE and PRISMA in the methodological framework previously identified [#37, #38]

Reply: We absolutely agree that this looks like a rather repetitive statement. Although the first (p. 12) refers to the reporting structure of the protocol (PRISMA-P) [42] and the second (p. 16) to the upcoming review (PRISMA) [46], it might appear as a redundancy to the reader. However, the two methodological papers that we cite throughout the manuscript do not refer to PRISMA guidelines, as that is an addition to ensure transparency, conformity with good reporting standards and fulfil the journal's requirements. Agreeing with you that this sounds repetitive, we thought of combining the above statements on p. 12, however, think that this might be confusing as we would miss that important element from Step 5 (collating, summarizing and reporting the results). We therefore decided to leave the statement as is with the hopefully acceptable trade-off of repetition.

FORMATTING AMENDMENTS (if any)
Required amendments will be listed here; please include these changes in your revised version:
.Supplementary file format
- Please re-upload your supplementary files in PDF format.

Reply: We have re-uploaded our supplementary files in PDF format.

VERSION 2 – REVIEW

REVIEWER	Isomi Miake-Lye VA Greater Los Angeles, USA
REVIEW RETURNED	29-Mar-2018

GENERAL COMMENTS	Thank you to the authors for their thoughtful and comprehensive responses. My concerns have been thoroughly addressed. However, as a minor point, the PRISMA checklist appears to be the old version still, since I do not see the "where to find" section the

	authors added.

REVIEWER	Martin Entwistle Ares Health Systems, USA
REVIEW RETURNED	24-Apr-2018

GENERAL COMMENTS	I participated in the first round review and it is gratifying to see many of the feedback comments have been addressed by the authors. In my view the paper has been significantly improved and is now in a publishable state, however I have a number of suggestions for further edits that would strengthen the paper. Abstract As the paper usefully makes use of a modified definition of existing published work on PGHD and that there is the risk of ambiguity around definition of other terms, I feel it would be useful for the Introduction to call out that the for the purposes of clear framing, the paper provides definitions of key terms used in the methodology. Strengths and Limitations Page 3 line 24, suggest modifying "As the review's scope of restricted to primary and secondary disease prevention ……." Page 3 line 30, if PROs are to be excluded in the definition of PGHD, it should be called out here as a limitation (See my comments on PROs in Methodology and Analysis. Background I remain concerned about the narrowing of scope of application of PGHD to prevention and health promotion. I accept that there are reasonable arguments for such narrowing, but the existence of a wider scope of application of PGHD exists and should be more clearly acknowledged along with an reference to the arguments provided in the Methods section which outline of the rationale for the more limited scoping. This issue is compounded by the existence of some ambiguity around the definition of "prevention" (see comments on this under Study Rationale). Unless the boundary between secondary and tertiary prevention is clearly articulated there is a risk of ambiguity around the scope of the material to be included in the review. This type of PGHD to be included in the review is defined as electronic PGHD. The definition is important and is provided later in the paper. Suggest making reference around page 5 line 49 to the existence of the definition in the methods section. In passing, the two examples of electronic PGHD page 5 line 49 and page 5 line 55 both fall in the realm of PGHD collected for clinical management, ie tertiary prevention, which is outside the declared scope of the review. The boundary between secondary and tertiary prevention is a grey area, which leads back to my concerns about narrowing the scope of the use of PGHD to exclude management! See my comments in the Methods section.

	Study Rationale No comments. Study Objectives No comments. Methods and Analysis Definition of electronic PGHD I feel the definition of the "electronic PGHD" can be further tightened. What does "digitally rooted" actually mean? For example does this term only mean PGHD that is captured in an electronic form from a device? Does it include patient entered data read from a device by an individual and manually entered into some type of submission form and in this way becomes digital? Consider a definition of electronic PGHD as being PGHD (as defined), that is available for use in a digital format, irrespective of how it is collected and communicated? Exclusion of PROs I do not believe PROs should be regarded as something other than PGHD and excluded. The authors may be interested to know that the ONCs definition of PGHD was intended to be broad and include PROs which they saw as falling in the ambit of "health-related data - including health history, symptoms, biometric data, treatment history, lifestyle choices, and other information……." The boundary between PGHD and PROs is another grey area, where exclusion has the potential to trigger edge-care debate, that would be avoidable if PROs are included in the scope of PGHD. In addition PROs have much to contribute to prevention and health promotion. Definitions of health promotion and prevention I've expressed my concerns about limitation of scope to primary and secondary prevention and health promotion. The authors have explained that the rationale is to make the review manageable and volume of literature and the time and resources to conduct a review is indeed a legitimate concern. However drawing a line between secondary and tertiary prevention will be problematic, which leads back to my concerns about narrowing the scope of the use of PGHD. The authors illustrate this very issue by providing two example of use of PGHD page 5 line 49 and page 5 line 55, both of which both fall in the realm of PGHD collected for clinical management, ie tertiary prevention. The authors should replace these examples with others that do illustrate use in primary or secondary prevention, or health promotion, to avoid confusion or dissonance for readers. Note that tertiary prevention is not limited to therapeutic interventions, but any ongoing active management of a clinical condition.

	Table 2 - Targeted PGHD Dimensions One aspect not addressed in the table of targeted PGHD dimensions is making the purposes for which PGHD was collected and then used explicit. At the current state of development there is significant use of PGHD for purposes other than for which it was collected and it would be useful for the review to be able to analyze this as is could have a significant bearing on a number of aspects of quality and use. For example, an individual may have collected steps for self-management in a weight program and the data is then used for a different program for example in exercise tolerance in heart failure prevention, but lack the necessary accuracy for clinical assessment. The authors could consider adding another row in the table of PGHD Dimensions "PGHD purpose and Use". With questions along the lines of "What was the intended purpose of collecting PGHD?" and "What was the actual use?" This suggested change may also need to be reflected in Table 4. Protocol Structure My previous concerns about review process and definition of roles and responsibilities have been addressed. See comments above on Targeted PGHD Dimensions in Methods and Analysis, which may have implications for Table 4. Ethics and Dissemination No comments. Acknowledgements No comments.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Comment 1: Thank you to the authors for their thoughtful and comprehensive responses. My concerns have been thoroughly addressed. However, as a minor point, the PRISMA checklist appears to be the old version still, since I do not see the "where to find" section the authors added.

Reply: Thank you very much for your time and your constructive feedback. Your input contributed significantly to the improvement of the protocol and thus, the upcoming review. We are very glad to hear that our revision has addressed all your previous concerns.

Regarding the PRISMA check-list, we will re-upload it, hoping that our “where to find” additions will be visible this time. Thank you very much.

Reviewer: 2

Comment 1: I participated in the first round review and it is gratifying to see many of the feedback comments have been addressed by the authors.

In my view the paper has been significantly improved and is now in a publishable state, however I have a number of suggestions for further edits that would strengthen the paper.

Reply: Thank you very much for the time you have put into reviewing our paper. All your comments have been very thoughtful and of paramount importance for the final result of the protocol, as well as the upcoming review. We very much appreciate that. Please find below our replies and corresponding changes to your suggestions. Thanks a lot.

Abstract

Comment 2: As the paper usefully makes use of a modified definition of existing published work on PGHD and that there is the risk of ambiguity around definition of other terms, I feel it would be useful for the Introduction to call out that the for the purposes of clear framing, the paper provides definitions of key terms used in the methodology.

Reply: Thanks a lot for this comment. We fully agree that providing definitions of key terms and concepts is crucial for all review steps and also agree that providing a clear is a core purpose of a protocol. We have added a sentence on p. 7 to hint towards that purpose.

p. 7 “Achieving that requires a clear framing, for which this protocol provides clear definitions of key terms and concepts.”

Strengths and Limitations

Comment 3: Page 3 line 24, suggest modifying "As the review's scope of restricted to primary and secondary disease prevention ……."

Reply: Great suggestion. We have indeed modified this statement, however, differently than suggested above, in order to bring it in line with the modifications we have made regarding the

definitions of prevention. You will find a detailed outline of these changes below, in the replies on your respective comments.

p. 3 “As the review’s scope is restricted to health promotion and certain dimensions of prevention, the resulting typology of electronic PGHD as well as the overall findings might not be applicable beyond those domains “

Comment 4: Page 3 line 30, if PROs are to be excluded in the definition of PGHD, it should be called out here as a limitation (See my comments on PROs in Methodology and Analysis.

Reply: Thanks for pointing out your concern regarding PROs. We fully acknowledge and share your view especially regarding the risk of debate if harshly excluding PROs. We outline our full response to this issue, as well as all corresponding protocol changes under your next PRO-related comment (under methods & analysis).

Background

Comment 5: I remain concerned about the narrowing of scope of application of PGHD to prevention and health promotion.

I accept that there are reasonable arguments for such narrowing, but the existence of a wider scope of application of PGHD exists and should be more clearly acknowledged along with an reference to the arguments provided in the Methods section which outline of the rationale for the more limited scoping.

This issue is compounded by the existence of some ambiguity around the definition of "prevention" (see comments on this under Study Rationale). Unless the boundary between secondary and tertiary prevention is clearly articulated there is a risk of ambiguity around the scope of the material to be included in the review.

Reply: Thanks a lot for your comment and thoughts on the review’s scope, as well as for acknowledging practical and feasibility challenges that are attached to a broader scope. We fully agree that having a specific focus should not leave the reader with the impression that anything that goes beyond that niche is of no relevance. Electronic PGHD are of high relevance for therapeutic, as well as rehabilitative processes, that we strongly hope future research will target and address. As you rightly suggest, to ensure that the readers get the right view on the broader applicability of PGHD, we

have articulated that in the background section of the protocol and created a linkage (reference) to our scope argumentation in the methods section.

p. 6 “Despite this study’s focus on prevention and health promotion, it is crucial to acknowledge the importance and applicability of electronic PGHD beyond those domains. In fact, such data can facilitate the treatment and rehabilitation of increasingly prevalent chronic conditions, such as diabetes and heart failure [17]. The justification for our limited scope has conceptual and practical reasons, outlined in the methods section. A more comprehensive and detailed definition of electronic PGHD is also outlined in the methods section of this protocol.”

We provide a full and detailed reply of the second part of your comment, regarding the definition on prevention under one of your following related comments under methods and analysis.

Comment 6: This type of PGHD to be included in the review is defined as electronic PGHD. The definition is important and is provided later in the paper. Suggest making reference around page 5 line 49 to the existence of the definition in the methods section.

Reply: We agree that the definition of electronic PGHD is crucial. We have therefore added a sentence, as suggested, pointing towards that definition. However, we felt that is somehow cuts the text flow on p. 5 line 49 and have therefore added it at the end of the study rationale section on p. 6.

p. 6 “A more comprehensive and detailed definition of electronic PGHD is also outlined in the methods section of this protocol.”

Comment 7: In passing, the two examples of electronic PGHD page 5 line 49 and page 5 line 55 both fall in the realm of PGHD collected for clinical management, ie tertiary prevention, which is outside the declared scope of the review. The boundary between secondary and tertiary prevention is a grey area, which leads back to my concerns about narrowing the scope of the use of PGHD to exclude management! See my comments in the Methods section.

Reply: Correct and very thoughtful statement. We have exchanged the two examples with more appropriate and clearly not tertiary prevention ones. We have also accordingly corrected the references in the reference list, deleting the old and exchanging them with the new examples.

p. 5-6 “For example, individuals at high risk of chronic disease, such as sedentary and overweight adults can self-monitor their physical activity at home and easily share their records on interactive, provider-connected online platforms, enabling professional feedback and guidance.[19] Similarly, they can self-capture overall health parameters, such as blood pressure, body fat or weight and rapidly

transmit their values via online-connected devices. Data sharing can trigger personalized feedback, customized health plans and other persuasive health promotion techniques.[20]”

Methods and Analysis

Definition of electronic PGHD

Comment 8: I feel the definition of the "electronic PGHD" can be further tightened. What does "digitally rooted" actually mean? For example does this term only mean PGHD that is captured in an electronic form from a device? Does it include patient entered data read from a device by an individual and manually entered into some type of submission form and in this way becomes digital? Consider a definition of electronic PGHD as being PGHD (as defined), that is available for use in a digital format, irrespective of how it is collected and communicated?

Reply: Excellent comment. As the focus of the review is on the use of such data for prevention/promotion purposes, we believe it is important that PGHD are in a digital format when actually being “used” for prevention and to promote health. To illustrate that: << collecting data using a pedometer, writing those on paper and hand the paper logs to a wellness coach that uses this paper logs to create a physical activity plan – would not be considered as digital PGHD >>. On the other hand, << measuring physical activity (with whatever means), entering those data in an app that is linked to a wellness coach who uses that information to provide feedback and plans, falls within the category of digital PGHD >>. Thus, crucial is that the data are in a digital format when actually utilized for prevention/promotion purposes, as your correctly suggested. We have amended the text to make that clearer.

On p. 10 we exchanged “digitally rooted” with “digital”

p. 10 “Accordingly, the term emphasizes digital “health-related data- including health history, symptoms, biometric data,…”

And further down on p. 10 we added the following sentence to tighten the definition:

p. 10 “To comply with our definition, PGHD should be available in a digital format when utilized for the intended health-related purposes.”

Exclusion of PROs

Comment 9: I do not believe PROs should be regarded as something other than PGHD and excluded. The authors may be interested to know that the ONCs definition of PGHD was intended to be broad and include PROs which they saw as falling in the ambit of "health-related data - including health history, symptoms, biometric data, treatment history, lifestyle choices, and other information……."

The boundary between PGHD and PROs is another grey area, where exclusion has the potential to trigger edge-care debate, that would be avoidable if PROs are included in the scope of PGHD. In addition PROs have much to contribute to prevention and health promotion.

Reply: Again, thanks a lot for mentioning that issue. Considering that the definition of PGHD seems to vary across papers, choosing one definition over another certainly requires clear justifications and awareness of the associated trade-offs. We certainly believe that PROs are PGHD and we believe it's wise to avoid the debate that would result by excluding them, simply based on them being labelled as PROs. In order to maintain our focus on PGHD that are primarily "patient-driven" we have instead decided to just differentiate our definition of PGHD from standardized, provider-defined and provider-driven PGHD, such as fixed questionnaires and surveys. That has two reasons. First, not keeping that focus would extend the size of our review by two – or threefold, which would deem difficult to manage, given the available time scope and resources. Second, although these standardized ways are crucial and very important, we would like to focus on a patient/consumer that is "empowered" and holds more responsibilities, which we believe is very important for effective prevention and health promotion. Fully agreeing with you and aiming to achieve a middle ground, we will not harshly exclude PROs from our definition, but instead focus on PGHD that offer some patient/consumer flexibility and responsibility. That has already been reflected in the strengths and limitations of the paper, which we therefore left as it is. However, we have accordingly amended the associated sections in the protocol.

p. 10 "Accordingly, the term emphasizes digitally rooted "health-related data- including health history, symptoms, biometric data, treatment history, lifestyle choices, and other information—created, recorded, gathered, or inferred by or from patients or their designees (i.e., care partners or those who assist them) to help address a health concern" and are captured outside traditional healthcare contexts. Our definition is limited to predominantly patient or consumer driven PGHD, being distinct from data collected through standardized, provider-driven questionnaires.[17, 36] Thus, responsibility for capturing, recording and sharing electronic PGHD lies with the patients and consumers.[17] We justify that focus on the very nature of prevention and health promotion, which requires an activated healthcare consumer."

Definitions of health promotion and prevention

Comment 10: I've expressed my concerns about limitation of scope to primary and secondary prevention and health promotion. The authors have explained that the rationale is to make the review manageable and volume of literature and the time and resources to conduct a review is indeed a legitimate concern.

However drawing a line between secondary and tertiary prevention will be problematic, which leads back to my concerns about narrowing the scope of the use of PGHD. The authors illustrate this very issue by providing two example of use of PGHD page 5 line 49 and page 5 line 55, both of which both fall in the realm of PGHD collected for clinical management, ie tertiary prevention.

The authors should replace these examples with others that do illustrate use in primary or secondary prevention, or health promotion, to avoid confusion or dissonance for readers.

Note that tertiary prevention is not limited to therapeutic interventions, but any ongoing active management of a clinical condition.

Reply: Thanks a lot for sharing your concern regarding the scope of the review, which is indeed tightly linked to the definition of prevention. This is also a challenge that we faced when initially drafting this protocol. There is no doubt that the definitions and boundaries of various prevention types/levels are neither clearly defined, nor uniform. In fact, those seem to change with different cultural backgrounds, different locations as well as from study to study. Acknowledging (1) the blurred boundaries between those fixed terms [primary – secondary – tertiary], (2) the missing consensus around their definitions, as well as (3) the practical challenges that we would face if we would widen the reviews scope, we have decided to re-articulate the scope section of the protocol, hopefully making the boundaries between the prevention aspects that we focus on and those that we don't more explicit. Our amendments outline those specific prevention aspects without significantly altering the review's scope. We hope and believe that these changes will reduce ambiguity regarding inclusion eligibility.

p. 11 "Acknowledging that the boundaries between primary, secondary and tertiary prevention, as well as their definitions are neither strictly defined nor clear, especially when it comes to complex chronic conditions, we set our study's limits around three precise prevention elements and health promotion.[39] Thus, to fall within the review's scope, studies require to be placed in the context of at least one of the following prevention domains: (1) preventing initial occurrence of disease in healthy or high-risk individuals, (2) mitigating risk in healthy or high-risk individuals, (3) monitoring ongoing disease that is free of apparent symptoms in order to avoid progression and (4) promoting health. Clinically managing ongoing disease that is manifested by experienced symptoms, discomfort or disability, therapeutic interventions and rehabilitation fall outside the review's focus. The reasoning for our narrowed scope is supported by conceptual and practical arguments. Conceptually, we follow Gordon's classification, that restricts the term prevention to primary and secondary levels. On the other hand, tertiary prevention follows after disease manifestation, which is in turn driven by different dynamics and often non-distinguishable from therapeutic activities.[39] Practically, keeping preventive and therapeutic interventions combined would enormously broaden up our review's scope and lead to an unmanageable amount of literature."

We also undertook a small change in the abstract, p. 2 to reflect that: ". Literature on prevention that is driven by existing discomfort or disability goes beyond the review's scope and will be excluded."

The other aspect of your comment regarding the provided examples has been addressed in one of your previous comments. Once again, thanks for this very constructive comment.

Table 2 - Targeted PGHD Dimensions

Comment 11: One aspect not addressed in the table of targeted PGHD dimensions is making the purposes for which PGHD was collected and then used explicit. At the current state of development there is significant use of PGHD for purposes other than for which it was collected and it would be useful for the review to be able to analyze this as is could have a significant bearing on a number of aspects of quality and use. For example, an individual may have collected steps for self-management in a weight program and the data is then used for a different program for example in exercise tolerance in heart failure prevention, but lack the necessary accuracy for clinical assessment.

The authors could consider adding another row in the table of PGHD Dimensions "PGHD purpose and Use". With questions along the lines of "What was the intended purpose of collecting PGHD?" and "What was the actual use?"

This suggested change may also need to be reflected in Table 4.

Reply: Thanks a lot for this valuable and very interesting addition. We agree that it would be interesting to get some insight on potential discrepancies between intentions of purpose and actual use. We have made some amendments to reflect this in tables 2 and 4, as suggested.

Table 2 p. 12-13 As we already had a "PGHD utilization" column, we added another one before that with the headline "PGHD purposes" and then added the comparison element within the utilization column. Please refer to the table.

Table 4 p. 18-19 Here we added an additional question under PGHD types to emphasize the focus on purposes, as well as an additional line that compares purposes and actual use. Please refer to the table.

Protocol Structure

Comment 12: My previous concerns about review process and definition of roles and responsibilities have been addressed.

See comments above on Targeted PGHD Dimensions in Methods and Analysis, which may have implications for Table 4.

Reply: We are glad to hear that our previous revision addressed all your previous concerns. We have considered the changes on dimensions and changed Table 4 (p. 18-19) accordingly, as outlined in our previous reply. Thank you very much.

VERSION 3 – REVIEW

REVIEWER	Martin Entwistle Ares Health Systems, USA
REVIEW RETURNED	14-Jun-2018

GENERAL COMMENTS	The authors are to be commended on their openness to feedback and to their willingness to assimilate this into edits to the draft paper, Having reviewed the last two drafts, and while the fundamental research approach has not changed from the concept originally submitted, I feel this paper now presents a much more robust description of the work proposed, along with the discussion of rationale, methods and limitations in a way that is educational for many. I hope the submitted paper can be published in the near future and the team embark on the research itself. I'm sure I will be one of many very interested to see the results of that work. On small point, Page 22 Line 24 states "Initiation of screening and data collection is planned for February 2018.", should this now be a future date or has the initiation process indeed begun?